Targeting Therapeutics to the Glomerulus With Nanoparticles

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Nanoparticles are an enabling technology for the creation of tissue-/cell-specific therapeutics that have been investigated extensively as targeted therapeutics for cancer. The kidney, specifically the glomerulus, is another accessible site for nanoparticle delivery that has been relatively overlooked as a target organ. Given the medical need for the development of more potent, kidney-targeted therapies, the use of nanoparticle-based therapeutics may be one such solution to this problem. Here, we review the literature on nanoparticle targeting of the glomerulus. Specifically, we provide a broad overview of nanoparticle-based therapeutics and how the unique structural characteristics of the glomerulus allow for selective, nanoparticle targeting of this area of the kidney. We then summarize literature examples of nanoparticle delivery to the glomerulus and elaborate on the appropriate nanoparticle design criteria for glomerular targeting. Finally, we discuss the behavior of nanoparticles in animal models of diseased glomeruli and review examples of nanoparticle therapeutic approaches that have shown promise in animal models of glomerulonephritic disease.

Key Words: Nanoparticles, Kidney, Glomerulus, Drug targeting, Glomerulonephritis

Introduction

Nanoparticles are an enabling technology for the creation of tissue-/cell-specific therapeutics. They have generated excitement in the cancer community because they can be designed to deposit more selectively in tumor tissues, thus minimizing the dose-limiting off-target effects associated with traditional, small-molecule-based drugs.[1] In addition to their higher therapeutic indexes, nanoparticles have been demonstrated to deliver significantly higher concentrations of drugs to target tissue compared with administration of free drug alone.[1,2] They have also enabled the application of new, high-specificity therapeutic modalities such as small interfering RNA (siRNA).[1,3]

Nanoparticles have been investigated extensively as targeted therapeutics for tumors and the liver because of their intrinsic proclivity to deposit in these tissues.[1,4] The kidney is another site of nanoparticle accumulation[5]; however, it has been relatively overlooked as a target organ for nanoparticle therapeutics. The incidence of ESRD in the United States is steadily increasing, mainly because of hypertension, diabetes, and glomerulonephritic diseases.[6,7] Each of these disease processes has significant pathology within the glomerulus. Pharmacologic intervention in all of these disease processes is limited by efficacy and toxicity. Targeting of the renin-angiotensin-aldosterone axis has been successful at slowing the rate of kidney decline, but not in the recovery of kidney function.[8,9] In addition, immunomodulating therapies in glomerulonephritic diseases are often limited because of systemic side effects. It is important to note that results have emerged that implicate that cells within the glomerulus (mesangial cells [MCs], podocytes, and endothelial cells) play major roles in the progression of these diseases.[10-13] Therefore, glomerular-targeted therapeutics are expected to have profound effects on these diseases. Given the medical need for the development of more potent, kidney-targeted therapies, the use of nanoparticle-based therapeutics may be one such solution to this problem.

Here, we have reviewed the literature on nanoparticle targeting of the glomerulus. The first section of this review provides a broad overview of nanoparticle-based therapeutics. We then delve into the unique structural characteristics of the glomerulus that allow for selective, nanoparticle targeting of this area of the kidney. Next, we summarize literature examples of nanoparticle delivery to the glomerulus and elaborate on the appropriate nanoparticle design criteria for glomerular targeting. We then discuss the behavior of nanoparticles in animal models of diseased glomeruli and discuss examples of therapeutic approaches that have shown promise in animal models of kidney disease. Finally, we speculate about the future of nanoparticles engineered to target glomerular diseases.

Design and Behavior of Nanoparticle-Based Therapeutics in the Body

Nanoparticle-based therapeutics are typically composed of a therapeutic entity such as a small-molecule drug, nucleic acid, or protein that is packaged together with structural components (eg, lipids or polymers) into nanosized objects.[1] There are also classes of nanoparticles composed of inorganic compounds such as gold, cadmium, or iron oxide that are also being investigated as therapeutics and imaging agents.[14,15] Nanoparticles such as liposomes, quantum dots, polyplexes, and lipoplexes are referred

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to by their composition rather than being referred to as nanoparticles. These entities are all examples of nanoparticles, and the principles governing their behavior in vivo are similar to other nanoparticle formulations.

Of note, this review focuses on systemically applied nanoparticles (ie, those nanoparticles that are administered intravenously or in some cases via intraperitoneal injection). Nanoparticles administered orally, topically, locally to tissue, or subcutaneously may exhibit altered pharmacokinetic/biodistribution properties than what is described below. However, regardless of administration route, the principles described below are applicable to any fraction of a nanoparticle dose that ends up in central circulation.

Nanoparticle-based therapeutics can overcome some of the traditional barriers to successful drug usage and development. The utility of traditional small-molecule-based therapeutics is often limited by their side effects; sufficiently high doses for optimal therapeutic activity may not be reached before a dose-limiting toxicity occurs. Development of small-molecule-based therapeutics can be stalled by the need to balance drug activity (pharmacodynamics) with the ability to be absorbed and distributed throughout the body (pharmacokinetics). Nanoparticle formulation of drugs offers an alternative to both of these key problems in drug usage and development. Because of their size, nanoparticle-based therapeutics have restricted distributions throughout the body (biodistribution).[1] Whereas small molecules can move freely across small gaps in the cells lining blood vessel walls (endothelial cells), nanoparticles require large spaces between endothelial cells to move from blood circulation into body tissues.[16] After dosing, nanoparticle-based therapeutics are trapped in the blood stream, except in tissues with fenestrated endothelia large enough to allow nanoparticle passage out of blood vessels into the tissue interstitia.[17]

CLINICAL SUMMARY

- Nanoparticles are therapeutics that can be designed for tissue-/cell-specific applications.
- Nanoparticles have an inherent proclivity for glomerular deposition that can be exploited for treating glomerular disease.
- Animal models have established proof of principle for nanoparticle delivery to glomeruli.

Endothelial barriers are often compromised in human disease such as cancer and inflammation. In these situations, nanoparticles can accumulate in pathologic tissue to a high extent while sparing the rest of the body from harmful side effects of their encapsulated drug. Some healthy tissues possess fenestrated endothelia that allow for passive accumulation of nanoparticles and are potential sites for nanoparticle off-target toxicity (if they are not the intended target of the therapy). These tissues are liver, spleen, and kidney.

Nanoparticle-based therapeutics are highly tunable and can be engineered for more precise drug delivery to desired sites of action based on the characteristics of the target tissue. Nanoparticle properties such as their size, surface composition (charge and cell surface receptor targeting-ligands), and decomposability can be tailored to specific applications. The behavior of nanoparticles in the body depends mostly on these 3 properties, regardless of the fundamental composition of the nanoparticle. Therefore, nanoparticles of any material and therapeutic payload can be rationally designed to behave in a desired manner in the body provided that the general characteristics (size, surface composition, decomposability) needed to behave in that desired manner are known.

Size is a major determinant of the circulation time and tissue deposition of a nanoparticle-based therapy. The circulation time of a nanoparticle depends on 3 factors: kidney excretion rate, tissue uptake rate, and nanoparticle degradation rate. The first 2 factors are largely dependent on size. Nanoparticles smaller than 10 nm are sufficiently small to pass through the kidney filtration barrier and enter the urine.[18] Nanoparticles above this size can have very long circulation times because they are not subject to first-pass kidney filtration unless they degrade into components smaller than 10 nm. The circulation times of nondecomposable nanoparticles is determined by their uptake by the reticuloendothelial system (RES).[19] RES nanoparticle uptake is largely determined by size, provided that nanoparticle surface charge is close to neutral. Nanoparticles from 10 to 200 nm primarily deposit in the liver where they are increasingly taken up by liver Kupffer cells with increasing nanoparticle size.[5] The spleen becomes the dominant nanoparticle sink for nanoparticles larger than 200 nm (the size cutoff for the fenestrations of the endothelium of liver sinusoids).

Nanoparticle surface composition can be engineered to alter tissue uptake and intratissue localization. The surfaces of nanoparticle therapeutics are in direct contact with the plasma and tissue milieu. The nature of these interactions can influence the behavior of the nanoparticles in the body and with each other. For example, nanoparticles with high surface charges tend to be more rapidly taken up the RES.[20] This phenomenon may be mediated by increased plasma protein binding to the surface of these particles or stronger interactions between the nanoparticles and the surface of the cells of the RES. In addition, the surface of nanoparticles can be engineered to encourage binding to specific plasma proteins that may facilitate their entry into non-RES cell types, such as hepatocytes.[21]

Using targeting ligands, the surfaces of nanoparticles can be engineered to encourage much more specific